

**WHAT IS CLAIMED IS:**

1. A method for gathering genetic information, the method comprising:
  - a) determining the identity of at least one nucleotide in the SIRT1 locus on human  
5 chromosome 10q of a subject; and
  - b) creating a record which includes information about the identity of the  
nucleotide and information relating to an Alzheimer's Disease (AD)-related parameter of the  
subject, wherein the AD-related parameter is other than the genotype of a nucleotide in the 10q  
AD6 region.  
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2. The method of claim 1 wherein the determining comprises evaluating a sample  
comprising human genetic material from the subject.
3. A method comprising:
  - a) evaluating a parameter of a SIRT1 molecule from a mammalian subject;  
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  - b) evaluating an Alzheimer's Disease (AD)-related parameter of the subject  
wherein the AD-related parameter is other than a parameter of a SIRT1 molecule; and
  - c) recording information about the SIRT1 parameter and information about the  
AD-related parameter, wherein the information about the parameter and information about the  
20 phenotypic trait are associated with each other in the database.
4. The method of claim 3 wherein the AD-related parameter is a phenotypic trait of  
the subject.
5. The method of claim 3 wherein the SIRT1 molecule is a polypeptide and the  
25 SIRT1 parameter comprises information about a SIRT1 polypeptide.
6. The method of claim 3 wherein the SIRT1 molecule is a nucleic acid and the  
SIRT1 parameter comprises information about identity of a nucleotide in the SIRT1 gene.  
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7. The method of claim 6, wherein the subject is an embryo, blastocyst, or fetus.

8. The method of claim 6, wherein the subject is a post-natal human, e.g., a child or an adult.

9. The method of claim 6, wherein step b) is performed before or concurrent with step a).

10. The method of claim 6, wherein the human genetic material comprises DNA and/or RNA.

11. The method of claim 6, further comprising:

c) comparing the SIRT1 parameter to reference information, e.g., information about a corresponding nucleotide from a reference sequence.

12. The method of claim 11, wherein the reference sequence is from a reference subject who has attained old age.

13. The method of claim 11, wherein the reference subject has attained at least 85 years of age.

14. The method of claim 11, wherein the reference subject did not exhibit AD.

15. The method of claim 11, wherein the reference subject was cognitively intact.

16. The method of claim 11, wherein the reference sequence is from a reference subject that has AD.

17. The method of claim 16, wherein the reference sequence is from a reference subject that has late-onset AD (LOAD).

18. The method of claim 6, further comprising:

c) comparing the nucleotide to a corresponding nucleotide from a genetic relative or family member.

19. The method of claim 11, further comprising:

d) evaluating risk or determining diagnosis of AD in the subject as a function of the genotype.

5           20. The method of claim 6, further comprising recording information about the SIRT1 parameter and AD-related parameter, e.g., in a database.

21. The method of claim 20, wherein the information is recorded in linked fields of a database.

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22. The method of claim 6, wherein the nucleotide is located in an exon, intron, or regulatory region of the SIRT1 gene.

15           23. The method of claim 6, wherein identity of at least one SNP from Table 1 is evaluated.

24. The method of claim 6, wherein a plurality of nucleotides in the SIRT1 locus are evaluated.

20           25. The method of claim 24, wherein at least 10 nucleotides are evaluated.

26. The method of claim 6, wherein a single nucleotide is evaluated.

25           27. The method of claim 6, wherein the evaluating of a SIRT1 parameter includes evaluating a nucleotide position in the SIRT1 locus on both chromosomes of the subject.

28. The method of claim 27, further comprising recording the information (e.g., as phased or unphased information).

30           29. The method of claim 11, further comprising aligning the genotyped nucleotides of the sample and the reference sequence.

30. The method of claim 11, further comprising identifying nucleotides that differ between the subject nucleotides and the reference sequence.

31. The method of claim 6, wherein the method is repeated for a plurality of subjects, the plurality comprising at least 50 subjects.

5 32. The method of claim 6, further comprising comparing the information of step a) and step b) to information in a database, and evaluating the association of the genotyped nucleotide(s) with AD.

10 33. The method of claim 6, wherein the AD-related parameter is a biochemical parameter.

34. The method of claim 33, wherein the biochemical parameter is an assessment of IGF-1, Ab42, tau, or vitamin B12.

15 35. The method of claim 34 wherein the assessment is of plasma, serum or cerebrospinal fluid (CSF).

20 36. The method of claim 35, wherein the biochemical parameter comprises information about plasma Ab42 levels, and wherein the evaluating comprises evaluating plasma Ab42 levels.

37. The method of claim 35, wherein the evaluating of an AD-related parameter comprises an immuno-assay.

25 38. The method of claim 6, wherein the AD-related parameter is an assessment of cognitive function.

30 39. The method of claim 38 wherein the AD-related parameter comprises a result of a mental examination, a memory test, a behavioral test, a personality test, or other cognitive test.

40. The method of claim 38 wherein the AD-related parameter comprises information about a symptom of dementia.

41. The method of claim 40 wherein the symptom of dementia comprises at least one of the following: decline in mental status; loss of recent memory; inability to learn and remember new information; behavioral disorganization; diminished abstract thinking; diminished judgment; and personality changes.

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42. The method of claim 6 wherein the AD-related parameter is an anatomical feature.

43. The method of claim 42 wherein the AD-related parameter comprises information about one or more of the following: a brain lesion or brain atrophy.

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44. The method of claim 6 wherein the AD-related parameter comprises information about a genetic polymorphism associated with AD other than a nucleotide polymorphism present in the SIRT1 locus.

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45. The method of claim 44 wherein the genetic polymorphism is a polymorphism of the ApoE gene.

46. The method of claim 44 wherein the genetic polymorphism is a nucleotide polymorphism, e.g., a SNP.

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47. The method of claim 44 wherein the nucleotide polymorphism is a nucleotide polymorphism in a gene encoding apoE, presenilin 1, presenilin 2, or APP.

48. The method of claim 6 further comprising making a decision about whether to provide an AD treatment as a function of the SIRT1 parameter.

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49. A computer-readable database that comprises a plurality of records, each record comprising:

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- a) a first field which comprises information about one or more nucleotides from a SIRT1 locus of a subject and;
  - b) a second field which comprises information about AD-related parameter of the subject.

50 The computer database of claim 49 wherein the AD-related parameter comprises information about a biochemical feature, anatomical feature, or cognitive assessment.

51 The computer database of claim 49 wherein the AD-related parameter is an AD  
5 diagnosis.

52. A method for gathering genetic information, the method comprising:

a) genotyping one or more nucleotides from a sample from a human subject, wherein the nucleotides are in a gene of a human SIR2 homolog; and

10 b) evaluating one or more features of Alzheimer's Disease (AD) in the subject.

53. A method for evaluating an AD-associated gene, the method comprising:

a) determining the identity of at least one nucleotide in the SIRT1 locus on human chromosome 10q for a plurality of subjects who have AD or are associated with AD; and

15 b) evaluating the distribution of one or more nucleotide identities for a given position in the SIRT1 locus among or between subjects of the plurality.

54. The method of claim 53 wherein evaluating the distribution further comprises comparing one or more nucleotide identities to corresponding nucleotides in subjects who do not  
20 have AD or who are not associated with AD.

55. A method for evaluating a compound, the method comprising:  
evaluating a compound for an effect on SIRT1 activity; and  
evaluating a compound for an effect on AD.

25 56. A method for evaluating a compound, the method comprising:  
for each compound of a plurality of compounds,  
evaluating the compound for an effect on SIRT1 activity; and  
if the compound has an effect on SIRT1 activity, evaluating the compound  
30 for an effect on AD.

57. The method of claim 56 wherein evaluating for an effect on SIRT1 activity comprises evaluating SIRT1 mRNA expression.

58. The method of claim 56 wherein evaluating for an effect on SIRT1 activity comprises evaluating a SIRT1 polypeptide.

59. The method of claim 56 wherein evaluating for an effect on SIRT1 activity  
5 comprises evaluating SIRT1 enzymatic activity.

60. The method of claim 56 wherein evaluating for an effect on SIRT1 activity comprises evaluating deacetylase activity.

10 61. The method of claim 60 wherein evaluating for an effect on SIRT1 activity comprises evaluating deacetylase activity for a SIRT1 specific substrate.

62. The method of claim 61 wherein evaluating for an effect on SIRT1 activity comprises evaluating deacetylase activity for an acetylated lysine amino acid, an acetylated  
15 peptide or acetylated protein.

63. The method of claim 62 wherein the acetylated peptide or acetylated protein comprises an acetylated amino acid sequence of at least 10 amino acid from a histone or p53.

20 64. The method of claim 56 wherein evaluating for an effect on AD comprises contacting the agent to a neuronal cell.

65. The method of claim 56 wherein evaluating for an effect on AD comprises contacting the agent to a mammal.  
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66. The method of claim 56 wherein evaluating for an effect on AD comprises contacting the agent to a mouse model of AD.

67. The method of claim 65 wherein evaluating for an effect on AD comprises testing  
30 the mammal with a cognitive test.

68. The method of claim 65 wherein evaluating for an effect on AD comprises evaluating the mammal for tangle formation.

69. The method of claim 56 wherein evaluating for an effect on AD comprises evaluating secretase activity.

70. The method of claim 56 wherein evaluating for an effect on AD comprises  
5 evaluating APP or a fragment thereof.

71. A method for evaluating an agent, the method comprising:  
providing a computer model of the structure of a compound and the structure of a  
SIRT1 protein;  
10 evaluating compatibility of the models; and  
evaluating a compound for an effect on AD.

72. The method of claim 71 wherein evaluating model compatibility comprises  
evaluating an energy potential.  
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73. The method of claim 71 wherein evaluating model compatibility comprises  
evaluating steric compatibility.

74. A method for treating or preventing Alzheimer's Disease (AD) in a subject, the  
20 method comprising:  
identifying a subject diagnosed with or at risk for AD; and  
administering to the subject an agent that modulates SIRT1 activity.

75. The method of claim 74 wherein the agent is administered in an amount effective  
25 to reduce apoptosis in the subject.

76. The method of claim 74, wherein the agent is administered in an amount effective  
to reduce amyloid plaque formation in the subject.

30 77. The method of claim 74, wherein the agent increases SIRT1 activity.

78. The method of claim 74, wherein the agent comprises a polyphenol.

79. The method of claim 74, wherein the agent comprises a stilbene or a chalcone.



80. The method of claim 79, wherein the agent comprises a trans-stilbene.

81. The method of claim 79, wherein the agent comprises a compound having the  
5 structure of Formula I.

82. The method of claim 79, wherein the agent comprises a compound having the  
structure of Formula II, III, or IV.

10 83. The method of claim 79, wherein the agent comprises a resveratrol.

84. The method of claim 79, wherein the agent comprises a compound selected from  
the group consisting of butein (3,4,2', 4'- tetrahydroxychalcone); piceatannol (3, 5, 3', 4'-  
tetrahydroxy-trans-stilbene); isoliquiritigenin (4,2',4'-trihydroxychalcone); fisetin (3,7,3',4'-  
15 tetrahydroxyflavone); and quercetin (3,5,7,3',4'-pentahydroxyflavone).

85. The method of claim 74, wherein the agent comprises a nucleic acid that encodes  
a SIRT1 polypeptide or a core domain thereof.

20 86. The method of claim 74, wherein the identifying comprises evaluating a feature  
for AD in the subject (e.g., a genetic, biochemical, anatomical, or cognitive feature or a symptom  
of AD).

87. The method of claim 86, wherein the feature of AD is a genetic polymorphism  
25 associated with AD.

88. The method of claim 87, wherein the genetic polymorphism is in the ApoE locus.

89. The method of claim 87, wherein the genetic polymorphism is in the SIRT1 gene.  
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90. The method of claim 74, wherein the identifying comprises evaluating one or  
more nucleotides in a SIRT1 nucleic acid of the subject (e.g., in the SIRT1 gene in the genome  
of the subject or in a SIRT1 RNA or cDNA).

91. A method for reducing AD-induced apoptosis in a cell, the method comprising: contacting the cell with an agent that increases SIRT1 activity.

92. The method of claim 91 wherein the cell is at risk for AD or from a subject at risk  
5 for or diagnosed with AD.

93. The method of claim 77 wherein the agent comprises a nucleic acid that encodes a SIRT1 polypeptide.

10 94. A method for evaluating a disorder, the method comprising:  
a) identifying a plurality of human individuals characterized by a disorder  
or having a genetic relationship with an subject characterized by the disorder;  
b) comparing distribution of a plurality of genetic markers among the  
subjects of the first plurality to distribution of markers of the plurality of genetic markers among  
15 subjects of a second plurality of human subjects, wherein the human subjects of the second  
plurality have attained at least 90, 95, 98, or 100 years of age.

95. The method of claim 94, wherein the plurality of genetic markers includes at least  
one, 10, 20, 30 or 50 markers from each chromosome.

20 96. The method of claim 94, wherein the plurality of genetic markers includes at least  
one marker from chromosome X.

97. The method of claim 96, wherein the plurality of genetic markers includes at least  
25 one marker in the SIRT1 gene.

98. The method of claim 94, further comprising evaluating a measure of linkage  
disequilibrium.

30 99. The method of claim 94, wherein each subject of the first plurality is suffering or  
at risk for an age-associated disorder.

100. The method of claim 94, wherein each subject of the first plurality is genetically  
related to an subject suffering or at risk for an age-associated disorder.

101. The method of claim 99 or 100, wherein the age-associated disorder is one of the following disorders: cancer; skeletal muscle atrophy; adult-onset diabetes; diabetic nephropathy, neuropathy; obesity; bone resorption; age-related macular degeneration, ALS, Bell's Palsy,  
5 atherosclerosis, cardiac diseases, chronic renal failure, type 2 diabetes, ulceration, cataract, presbiopia, glomerulonephritis, Guillan-Barre syndrome, hemorrhagic stroke, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, SLE, Crohn's disease, osteoarthritis, Parkinson's disease, pneumonia, and urinary incontinence.

10 102. The method of claim 99 or 100, wherein the age-associated disorder is Alzheimer's disease.

103. The method of claim 94, wherein the first plurality includes at least 50, 100, 150,  
200, or 300 subjects.

15 104. The method of claim 94, wherein the human subjects of the second plurality are free of an AD diagnosis.

105. The method of claim 94, wherein the human subjects of the second plurality are  
20 cognitively intact at the age of 85, 90, 95, 98, or 100.

106. The method of claim 94, wherein the human subjects of the second plurality are free of a symptom or diagnosis of the disorder.

25 107. The method of claim 94, wherein the second plurality includes at least 50, 100, 150, 200, 300, 500 or 800 subjects.